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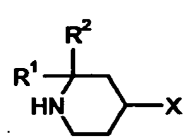
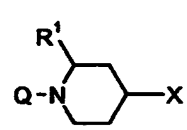
(54) Title: A PROCESS FOR THE REGIOSELECTIVE SYNTHESIS OF 2,2-DIALKYL-4-SUBSTITUTED PIPERIDINES



(I)



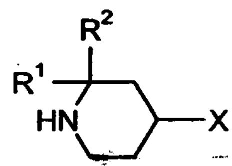
(II)

(57) Abstract: The present invention provides a process for preparing a compound of formula (I): wherein R^1 and R^2 each independently represent C_1-C_4 alkyl; and X represents an alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle, comprising treating a compound of formula (II): wherein Q represents Cl or Br, with a suitable base followed by addition of a suitable Lewis acid and addition of a compound of formula R^-M^+ wherein M^+ is a suitable cation.

A PROCESS FOR THE REGIOSELECTIVE SYNTHESIS OF 2,2-DIALKYL-4-SUBSTITUTED PIPERIDINES

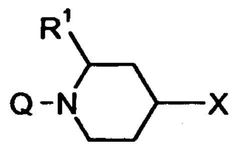
The present invention allows for regioselectively preparing 2,2-dialkyl-4-substituted piperidines. The present invention provides an efficient synthesis of various 2,2-dialkyl-4-substituted piperidines which are useful intermediates in the preparation of pharmaceuticals.

The present invention provides a process for preparing a compound of formula I:



formula I

wherein R^1 and R^2 each independently represent C_1-C_4 alkyl; and X represents an alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle, comprising treating a compound of formula II:



formula II

wherein Q represents Cl or Br, with a suitable base followed by addition of a suitable Lewis acid and a compound of formula R^-M^+ wherein M^+ is a suitable cation.

In addition, the present invention provides novel compounds which are prepared by the process of the present invention.

As used herein, the terms "Me", "Et", "Pr", "iPr", "Bu" and "t-Bu" refer to methyl, ethyl. propyl, isopropyl, butyl and tert-butyl, respectively.

As used herein, the terms "Halo", "Halide" or "Hal" refer to a chlorine, bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein the term "alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain. It is understood that the term "alkyl" includes within its definition the terms "C_1-C_{20} alkyl", "C_1-C_{10} alkyl", "C_1-C_6 alkyl", and "C_1-C_4 alkyl".

As used herein the term "C_1-C_4 alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "C_1-C_6 alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like.

As used herein the term "C_1-C_{10} alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 10 carbon atoms and includes, but is not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like.

As used herein the term "C_1-C_{20} alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 20 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, 3-methylpentyl, 2-ethylbutyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-nonadecyl, n-eicosyl and the like.

As used herein the term "C_1-C_6 alkoxy" refers to a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the term "C_1-C_4 alkoxy".

As used herein the term "halo(C_1-C_6)alkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms with 1, 2 or 3 halogen atoms attached to it. Typical halo(C_1-C_6)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-t-butyl, trifluoromethyl and the like. The term "halo(C_1-C_6)alkyl" includes within its definition the term "halo(C_1-C_4)alkyl".

As used herein the term "cycloalkyl" refers to a saturated hydrocarbon ring structure. It is understood that the term "cycloalkyl" includes within its definition the term "C_3-C_8 cycloalkyl". Typical C_3-C_8 cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

As used herein the term "alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain. It is understood that the term "alkenyl" includes within its definition the term "C_2-C_6 alkenyl". Typical C_2-C_6 alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

As used herein the term "aryl" refers to a monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like.

As used herein the term "heterocycle" refers to a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated or unsaturated, and consists of carbon atoms and from one to three heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized and including a bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which affords a stable structure.

Examples of such heterocycles include piperidinyl, piperazinyl, azepinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl-sulfoxide, thiamorpholinylsulfone, oxadiazolyl, triazolyl, tetrahydroquinolinyl, tetrahydrisoquinolinyl, and the like.

The term "substituted" as used in the term "substituted aryl" and "substituted heterocycle" signifies that one or more (for example one or two) substituents may be present on the aryl or heterocycle. Examples of substituents which may be present are H, F, Cl, Br, I, C_1-C_6 alkyl,

C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, phenyl, NO_2, NH_2, CN, or phenyl substituted with from 1 to 3 substituents selected from the group consisting of F, Cl, Br, I, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, phenyl, NO_2, NH_2, and CN.

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As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most

especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formulas I or Ia can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

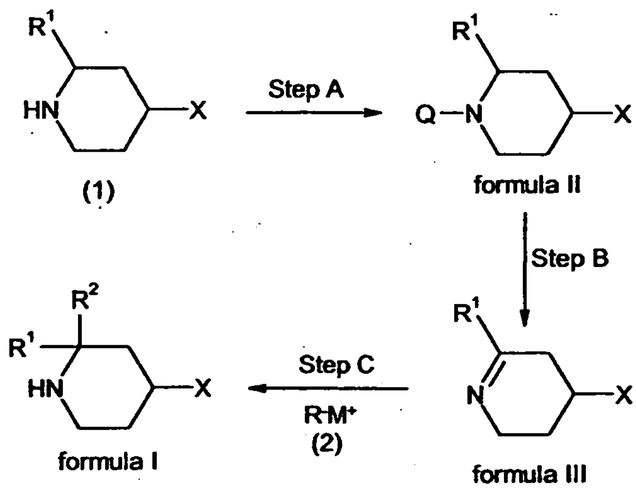
The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

The specific stereoisomers and enantiomers of compounds of formula (I) can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7, Separation of Stereoisomers. Resolution. Racemization, and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, the specific stereoisomers and enantiomers can be prepared by

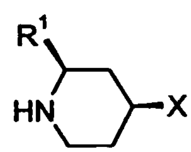
stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

The compounds of formula I can be prepared by following the procedures as set forth in Scheme I. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

Scheme I



In Scheme I, step A, the compound of structure (1) is treated with a suitable N-chlorinating reagent or an N-brominating reagent, which are well known in the art, to provide the compound of formula II. It is preferred that the compound of structure (1) be in the CIS configuration (1') as shown below for structure (1'):



(1')

Examples of suitable N-chlorinating reagents are N-chlorosuccinimide, sodium hypochlorite, t-butylhypochlorite, N-chlorophthalimide, N-bromosuccinimide, and the like. N-chlorosuccinimide is the preferred N-chlorinating reagent. For example, compound (1) is dissolved in a suitable organic solvent, such as diethyl ether and tetrahydrofuran and treated with about 1 equivalent of N-chlorosuccinimide. The reaction mixture is stirred at room temperature for about 30 minutes to 16 hours and the product, compound of formula II, is then isolated by standard techniques well known in the art, such as extraction techniques. For example, the reaction is diluted with saturated aqueous sodium bicarbonate and water, and then extracted with diethyl ether or methyl tert-butyl ether. The

organic extracts are combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the compound of formula II.

In Scheme I, step B, the compound of formula II is dehydrohalogenated with a suitable base in the presence of a suitable crown ether to provide the imine of formula III. Examples of suitable bases are potassium hydroxide, potassium superoxide, and the like. Potassium hydroxide is the preferred suitable base. Examples of suitable crown ethers are 18-crown-6, dibenzo-18-crown-6, and the like. 18-crown-6 is the preferred crown ether. In addition, in Scheme I, step B, the compound of formula II can be dehydrohalogenated with a suitable base which does not require addition of a suitable crown ether, to provide the imine of formula III. Examples of such suitable bases which do not require a suitable crown ether include aqueous sodium hydroxide, Amberlyst® A-27 in THF with no water present, potassium tert-butoxide, lithium tert-butoxide, lithium diisopropylamide (LDA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the like.

For example, the compound of formula II is dissolved in a suitable organic solvent, such as tetrahydrofuran and treated with about 0.05 equivalents to about 1.0 equivalents of a crown ether, such as 18-crown-6, with about 0.073 equivalents of crown ether being preferred. The solution is then treated with about 2 equivalents to about 3 equivalents of a suitable base in water, such as potassium hydroxide, with 3 equivalents of suitable base being preferred. The reaction mixture is stirred at room temperature for about 8 to 24 hours and the resulting imine of formula III is isolated by techniques well known in the art, such as drying over anhydrous sodium sulfate and filtering to provide the imine of formula III in solution.

Alternatively, in Scheme I, step B, the compound of formula II is dissolved in a suitable organic solvent, such as tetrahydrofuran and treated with about 2 equivalents to about 3 equivalents of a suitable base, such as DBU, lithium tert-butoxide or lithium diisiopropylamide. The reaction mixture is stirred for about 8 hours to about 24 hours at room temperature, and the resulting imine is isolated by techniques well known in the art, such as extraction, to provide the imine of formula III.

In Scheme I, step C, the imine of formula III is treated with a suitable Lewis acid, such as boron trifluoride etherate and then alkylated with a compound of structure (2) wherein M+ is a suitable cation, such as lithium. Examples of compounds of structure (2) are methyllithium, butyllithium, and the like. For example, an excess of the compound of structure (2), such as methyl lithium in a suitable organic solvent, such as diethyl ether, is cooled to about -25°C to about room temperature with about –10°C being preferred. The imine of formula III in tetrahydrofuran is cooled to about –25 °C to –78 °C and treated with boron trifluoride etherate. The cooled solution of compound (2) is then added to the solution of the boron trifluoride complex of the imine and stirred 4 to 16 h. The crude compound of formula I is isolated by standard extractive techniques. For example, the reaction is diluted with water and the resulting layers are separated. The aqueous phase is extracted with diethyl ether or methyl tert-butyl ether, the organic layer and organic extracts are combined, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the compound of formula I. The compound of formula I is then optionally purified by techniques well known in the art, such as chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexanes.

The following examples are illustrative only and represent typical syntheses of the compounds of formula I as described generally above. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "eq" or "equiv." refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "µL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "min" refers to minutes; "h" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ" refers to parts per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to *N,N*-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "aq" refers to

aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to methyl tert-butyl ether, and "RT" refers to room temperature.

Preparation 1

Preparation of (±)-*N,N*-Dimethyl-2-(2-ethylphenyl)-2-hydroxythioacetamide.

A solution of 30.11 g of 1-bromo-2-ethylbenzene in ca. 500 mL of freshly distilled THF was treated with 112 mL of 1.6 M *n*-BuLi in hexanes at –78 °C over a period of ca. 3h. To this was added 15 mL of anhydrous DMF, and the mixture was stirred at –78 °C for 30 min. The cold bath was removed, and the reaction was quenched with ca. 300 mL of saturated aqueous NH_4Cl. The layers were separated, and the organic layer was washed with ca. 300 mL of brine. The aqueous layers were back extracted with 2 x 500 mL of EtOAc. Combined organic layers were dried over $MgSO_4$, concentrated, and dried under vacuum to yield 20.89 g (96%) of fairly clean crude 2-ethylbenzaldehyde.

To 29.0 mL of diisopropylamine in ca. 500 mL of freshly distilled THF at –70 °C was added 117 mL of 1.6 M *n*-BuLi in hexanes, and the yellow solution was stirred at –70 °C for 20 min, for 15 min without the cold bath, then re-cooled to –73 °C. To this was added a pre-cooled (-70 °C) mixture of 20.89 g of the crude benzaldehyde and 16 mL of *N,N*-dimethylthioformamide in 70 mL of freshly distilled THF via a cannula over 15 min. The reddish clear solution was stirred at –75 °C for 45 min, then the cold bath was removed, and the mixture was stirred for another 30 min. The reaction was quenched with ca. 300 mL of saturated aqueous NH_4Cl, and the layers were separated. The aqueous layer was extracted with 3 x 500 mL of EtOAc. The organic layers were washed with ca. 300 mL of brine, combined, dried over $MgSO_4$, and concentrated. The residue was crystallized from EtOAc-hexanes to afford 25.20 g (73%) of yellowish crystalline solid. IR ($CHCl_3$) ~3200 (br), 3009, 1529, 1387 cm^{-1}. mp 104-105 °C. Ion Spray MS 223.9 $(M+H)^+$. $C_{12}H_{17}NOS$

Analysis:	calculated	found
C	64.54	64.70
H	7.67	7.73
N	6.27	6.31

Preparation of 4-Ethyl-2-(*N*,*N*-dimethylamino)benzo[*b*]thiophene.

N,*N*-Dimethyl-2-(2-ethylphenyl)-2-hydroxythioacetamide (25.1 g, 112 mmol) was dissolved in Eaton's reagent (7.5% w/w $P_2O_5/MeSO_3H$) (330 mL). The reaction mixture was heated to 80 °C and stirred for 1 h. The reaction mixture was then cooled to room temperature and stirred for an additional 1.5 h. The reaction was quenched by pouring the reaction mixture slowly into cooled (0 °C) 5.0 N NaOH (1.60 L). The mixture was extracted with EtOAc (2 x 1.50 L). The combined organic layers were then dried over $MgSO_4$ and concentrated to yield the title benzo[*b*]thiophene (21.66 g, 94% crude yield) as a red oil. EIMS 205 M^+; 190 $(M-15)^+$ (base peak).

^{1}HNMR ($CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 5.98 (s, 1H), 3.01 (s, 6H), 2.82 (q, *J* = 7.8 Hz, 2H), 1.30 (t, *J* = 7.8 Hz, 3H).

Preparation of 4-Ethylthianapthen-2-one.

4-ethyl-2-dimethylaminobenzo[*b*]thiophene (11.10g, 54.0 mmol) was dissolved in a 1:1 mixture of THF/1.0 N HCl (380 mL). The biphasic mixture was stirred vigorously and heated at reflux for 3 h 15 min. The reaction mixture was then cooled to room temperature and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 400 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 4-ethylthianapthen-2-one (9.63 g, quantitative crude yield) as a dark red solid.

^{1}HNMR ($CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 3.82 (s, 2H), 2.51 (q, *J* = 7.8 Hz, 2H), 1.17 (t, *J* = 7.8 Hz, 3H).

Preparation of 4-Ethylbenzo[*b*]thiophene.

To a solution of 4-ethylthianapthen-2-one (19.5 g, 110 mmol) in CH_2Cl_2 (1.15 L) was added dropwise 1.0 M diisobutylaluminum hydride in toluene (150 mL, 150 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h. The reaction was quenched with conc. HCl (700 mL) added dropwise over a period of 1.5 h. This mixture was then stirred vigorously for 2 h. The layers were separated, and

the organic layer was washed with brine (1 x 500 mL), dried over $MgSO_4$ and concentrated. The residue was purified by medium pressure chromatography (100% hexanes) to give 4-ethylbenzo[*b*]thiophene as a yellow oil (6.37 g, 37%). EIMS 162 M^+.

^{1}HNMR ($CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 6.4 Hz, 1H), 6.98 (distorted d, 2H), 2.80 (q, *J* = 7.8 Hz, 2H), 1.15 (t, *J* = 7.8 Hz, 3H).

Preparation of *N-t*-Butoxycarbonyl-4-(4-ethylbenzo[*b*]thiophen-2-yl)-2-methyl-4-piperidinol.

To a solution of 4-ethylbenzo[*b*]thiophene (6.37 g, 39.2 mmol) in dry THF (200 mL) at -78 °C was added 1.6 M *n*-BuLi in hexanes (27.0 mL, 43.2 mmol). The solution was stirred at -78 °C for 2 h. *N-t*-Butoxycarbonyl-2-methyl-4-piperidone (6.70 g, 31.4 mmol) dissolved in THF (20 mL) was added via a cannula at -78 °C. The reaction mixture was stirred at -78 °C for 3 h. The reaction was then quenched with 200 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (1 x 200 mL). The combined organic layers were then dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by medium pressure chromatography (20% EtOAc/hexanes) to give *N-t*-butoxycarbonyl-4-(4-ethylbenzo[*b*]thiophen-2-yl)-2-methyl-4-piperidinol as a white foam (6.58 g, 56%). IR ($CHCl_3$) 3425 (br), 1664, 1692 cm^{-1}. Ion Spray MS 376 $(M+H)^+$; 302 $(M-73)^+$ (base peak); 434 $(M+CH_3COO^-)^-$. $C_{21}H_{29}NO_3S$

analysis:	calculated	found
C	67.17	66.94
H	7.78	7.91
N	3.73	3.91

Preparation of (±)-*cis*-4-(4-Ethylbenzo[*b*]thiophen-2-yl)-2-methylpiperidine.

To a solution of *N-t*-butoxycarbonyl-4-(4-ethylbenzo[*b*]thiophen-2-yl)-2-methyl-4-piperidinol (6.58 g, 17.5 mmol) in dry CH_2Cl_2 (60 mL) at 0 °C was added 25 mL of trifluoroacetic acid. The solution was stirred at 0 °C for 1.5 h. The reaction was then quenched at room temperature with saturated aqueous $NaHCO_3$ solution (260 mL). The mixture was extracted with CH_2Cl_2 (1 x 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield 5.90 g of crude regioisomeric olefins. To a solution of the crude olefins (5.90 g) in a 3:1 mixture of ethanol (135 mL) and 2,2,2-trifluoroethanol (40 mL) was

added 10% Pd/C (4.50 g). The black slurry was stirred vigorously at room temperature under hydrogen (balloon pressure) for 72 h. The black slurry was then filtered over a pad of diatomaceous earth and washed with ethanol. The filtrate was concentrated, and the residue was purified by medium pressure chromatography [silica gel, 4% (3.5 M NH_3 in MeOH)/CH_2Cl_2] to give *cis*-(±)-4-(4-ethylbenzo[*b*]thiophen-2-yl)-2-methylpiperidine as a yellow semi-solid (2.37 g, 52%).

Preparation 2

Preparation of 2-Fluorobenzenethioacetaldehyde diethyl acetal.

The title compound was prepared in quantitative crude yield from 2-fluorobenzenethiol by essentially following the procedures detailed in (Graham, S.L., et. al. *J. Med. Chem.* 1989,32, 2548-2554).

Preparation of 7-Fluorobenzo[*b*]thiophene.

To a biphasic mixture of polyphosphoric acid (PPA; 43.0 g) and 385 mL of dry chlorobenzene heated to reflux, was added dropwise 2-fluorobenzenethioacetaldehyde diethyl acetal (19.1 g, 78.1 mmol) in 60 mL of chlorobenzene over a period of 2.5 h. The reaction mixture was cooled to room temperature and the organic layer was decanted off the PPA layer. The PPA layer was cooled to 0 °C and diluted with 400 mL of H_2O. This aqueous layer was extracted with Et_2O (2 x 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by a medium pressure chromatography system (silica gel, 100% hexanes) to afford 7-fluorobenzo[*b*]thiophene as a yellow oil (5.42 g, 46%). FDMS m/e=152 (M^+).

^{1}HNMR ($CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 5.4 Hz, 1H), 7.36 (dd, *J* = 5.4, 3.9 Hz, 1H), 7.31 (dt, *J* = 7.8, 4.9 Hz, 1H), 7.03 (dd, *J* = 9.8, 7.8 Hz, 1H).

Preparation of *N-t*-Butoxycarbonyl-4-(7-fluorobenzo[*b*]thiophen-2-yl)-2-methyl-4-piperidinol.

To a solution of 7-fluorobenzo[*b*]thiophene (4.00 g, 26.3 mmol) in dry THF (130 mL) at -78 °C was added 1.6 M *n*-BuLi in hexanes (18.1 mL, 28.9 mmol). The solution was stirred at -78 °C for 50 min. *N-t*-Butoxycarbonyl-2-methyl-4-piperidone (5.61 g, 26.3 mmol) dissolved in THF (20 mL) was added via a cannula at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. The reaction was then quenched with 110 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (2 x 400 mL). The combined organic layers were then dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by medium pressure chromatography (15% EtOAc/hexanes) to give *N-t*-butoxycarbonyl-4-(7-fluorobenzo[*b*]thiophen-2-yl)-2-methyl-4-piperidinol as a white foam (5.90 g, 61%). IR ($CHCl_3$) 3350 (br), 1680 cm^{-1}. Ion Spray MS 205 $(M-160)^+$; 366 $(M+H)^+$; 424 $(M+CH_3COO^-)^-$. $C_{19}H_{24}FNO_3S$

analysis:	calculated	found
C	62.44	62.14
H	6.62	6.92
N	3.83	3.90

Preparation of (±)-*cis*-4-(7-Fluorobenzo[*b*]thiophen-2-yl)-2-methylpiperidine.

To a solution of *N-t*-butoxycarbonyl-4-(7-fluorobenzo[*b*]thiophen-2-yl)-2-methyl-4-piperidinol (5.90 g, 16.1 mmol) in dry CH_2Cl_2 (56 mL) at 0 °C was added 24 mL of trifluoroacetic acid. The solution was stirred at 0 °C for 1 h. The reaction was then quenched at room temperature with saturated aqueous $NaHCO_3$ solution (280 mL). The mixture was extracted with CH_2Cl_2 (2 x 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield 3.84 g of crude regioisomeric olefins. To a solution of the crude olefins (3.84 g) in a 3:1 mixture of ethanol (110 mL) and 2,2,2-trifluoroethanol (37 mL) was added 10% Pd/C (4.00 g). The black slurry was stirred vigorously at room temperature under hydrogen (balloon pressure) for 16 h. The black slurry was then filtered over a pad of diatomaceous earth and washed with ethanol. The filtrate was concentrated, and the residue was purified by medium pressure chromatography [silica gel, 4-5% (3.5 M NH_3 in MeOH)/CH_2Cl_2] to give *cis*-(±)-4-

(7-fluorobenzo[*b*]thiophen-2-yl)-2-methylpiperidine as a brown solid (1.45 g, 36%). mp 55-57 °C.

Preparation 3

Preparation of 1-(t-Butyloxycarbonyl)-4-(6-methoxynaphth-2-yl)-2-methylpiperidin-4-ol.

To a solution of 2-bromo-6-methoxynaphthalene (13.009 g, 54.9 mmol) in tetrahydrofuran (400 mL) at –78 °C was added dropwise *t*-butyllithium (71.0 mL, 0.121 mol). After 30 minutes at –78 °C, a solution of 1-(*t*-butyloxycarbonyl)-2-methyl-4-piperidone (12.87 g, 60.4 mmol) in tetrahydrofuran (50 mL) was added dropwise. The mixture was stirred at –78 °C for 4 hours and then diluted with saturated ammonium chloride and extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (dichloromethane / 2% methanol in dichloromethane gradient eluent) to give 5.81 g (29%) of the title compound as a yellow oil. FDMS m/e = 362 (M^{+}+1).

Preparation of 4-(6-Methoxynaphth-2-yl)-2-methyl-1,2,3,6-tetrahydropyridine.

1-(*t*-Butyloxycarbonyl)-4-(6-methoxynaphth-2-yl)-2-methylpiperidin-4-ol (5.795 g, 8.79 mmol) was suspended in toluene (100 mL) and p-toluenesulphonic acid hydrate (5.016 g, 26.4 mmol) was added. The mixture was heated at reflux for 2 hours, then cooled to room temperature. The mixture was evaporated and the residue was diluted with 2 N sodium hydroxide, then extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and evaporated to give the title compound as a yellow oil (3.95 g, 100%). FDMS m/e = 254 (M^{+}+1).

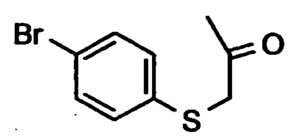
Preparation of (*cis*)-4-(6-Methoxynaphth-2-yl)-2-methylpiperidine.

To a solution 4-(6-Methoxynaphth-2-yl)-2-methyl-1,2,3,6-tetrahydropyridine (3.9 g, 15.4 mmol) in ethanol (200 mL) and 2,2,2-trifluoroethanol (70 mL) was added 10% palladium on carbon (400 mg). The mixture was stirred under one atmosphere of hydrogen for 19 hours. The

mixture was filtered and the catalyst was washed with boiling methanol. The combined organic layers were evaporated and the residue was purified by silica gel chromatography (dichloromethane / 5% methanol, 0.35 M ammonia in dichloromethane gradient elution) to give the *cis* isomer, (1.97 g, 50%) as a yellow amorphous solid. FDMS m/e = 256 (M^{+}+1).

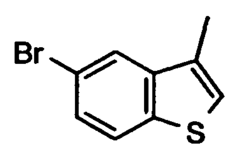
Preparation 4

Preparation of:



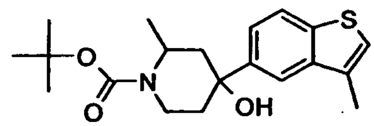
To 24.1 g (0.12 mol) of 4-bromothiophenol was added 168 mL of H_2O and 5.6 g (0.13 mol) of NaOH beads. To the resulting slurry was added 11.8 g (0.12 mol) of chloroacetone over 10 min. After 2.5 h, the product was removed by filtration and rinsed with H_2O. After drying under vacuum at 35 °C for 3 days, 29.5 g (99%) of title compound was obtained as an off-white solid.

Preparation of 5-bromo-3-methylbenzo[*b*]thiophene.



Amberlyst-15 resin (10 g) was slurried in 75 mL of chlorobenzene and the mixture was heated to reflux. Solvent was distilled and fresh solvent was added at an equal rate until 100 mL of solvent had been collected. A solution of 10.0 g (0.041 mol) of the ketone prepared in preparation 7 above in 50 mL of chlorobenzene was added dropwise over 3 h. Solvent was removed by distillation during the addition and 80 mL of additional chlorobenzene was added to maintain a constant volume. The mixture was allowed to cool room temperature and filtered. The resin was rinsed with 50 mL of chlorobenzene and the filtrate was evaporated to 9.38 g (100%) of title compound.

Preparation of 1-(*t*-Butyloxycarbonyl)-2-methyl-4-(3-methylbenzo[b]thiophen-5-yl)-piperidin-4-ol.



To a solution of 5-bromo-3-methylbenzo[*b*]thiophene (3.621 g, 15.9 mmol, from preparation 8) in diethyl ether (100 mL) was added magnesium (0.775 g, 31.9 mmol) and 1,2-dibromoethane (1.37 mL, 15.9 mmol). The mixture was heated at reflux for 4 hours then cooled to 20 °C for 18 hours. A solution of 1-(*t*-butyloxycarbonyl)-2-methyl-4-piperidone (3.74 g, 17.5 mmol) in tetrahydrofuran (15 mL) was added dropwise to the mixture. The mixture was stirred for 24 hours, then diluted with saturated ammonium chloride and extracted with ethyl acetate three times. The residue was purified by silica gel chromatography (dichloromethane / 5% methanol in dichloromethane gradient eluent) to give 4.36 g (76%) of the intermediate title compound as a yellow amorphous solid. FDMS m/e = 362 (M^{+}+1).

Preparation of 2-Methyl-4-(3-methylbenzo[*b*]thiophen-5-yl)-1,2,3,6-tetrahydropyridine.

1-(*t*-Butyloxycarbonyl)-2-methyl-4-(3-methylbenzo[*b*]thiophen-5-yl)-piperidin-4-ol (26.08 g, 72.1 mmol) was suspended in toluene (700 mL) and *p*-toluenesulphonic acid hydrate (41.17 g, 0.216 mol) was added. The mixture was heated at reflux for 3 hours, then cooled to room temperature. The mixture was evaporated and the residue was diluted with 2 N sodium hydroxide then extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and evaporated to give the title compound as a yellow oil (14.3 g, 81%). FDMS m/e = 244 (M^{+}+1).

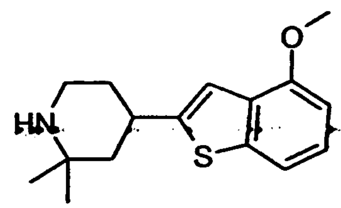
Preparation of (*cis*)-2-Methyl-4-(3-methylbenzo[b]thiophen-5-yl)piperidine.

To a solution 2-Methyl-4-(3-methylbenzo[*b*]thiophen-5-yl)-1,2,3,6-tetrahydropyridine (4.422 g, 18.2 mmol) in methanol (30 mL) was added 3% palladium on polyethylenimine/SiO_2 (4.9 g). The mixture was hydrogenated on a PARR shaker at 50 °C and 45 psi for 24 hours. At this time another 6 g of 3%

palladium on polyethylenimine/SiO_2 was added and the mixture was hydrogenated for 48 hours at 50 °C and 45 psi. The mixture was cooled and then filtered and the catalyst was washed with boiling methanol. The combined organic layers were evaporated and the residue was purified by silica gel chromatography (dichloromethane / 5% methanol, 0.35 M ammonia in dichloromethane gradient elution) to give the *cis* title compound (1.9 g, 43%) as a yellow oil.

Example 1

Preparation of 2,2-Dimethyl-4-(4-methoxybenzo[*b*]thiophen-2-yl)piperidine.



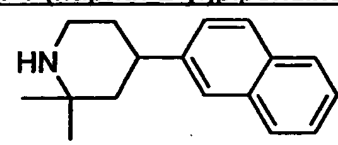
Scheme I, step A: A solution of *cis*-(±)-4-(4-methoxybenzo[*b*]thiophen-2-yl)-2-methylpiperidine in THF (35 mL) was cooled to 0 °C (ice-water bath), then treated with *N*-chlorosuccinimide (2.26 g, 16.94mol). After stirring 15 minutes, the ice-water bath was removed and the mixture was stirred at room temperature for 45 minutes. The mixture was then concentrated under reduced pressure and diluted with Et_2O (100 mL), saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL). The mixture was shaken and partitioned in a separatory funnel. The aqueous layer was separated and extracted once with Et_2O. The combined organic layers were washed once with H_2O (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the *cis*-(±)-*N*-chloro-4-(4-methoxybenzo[*b*]thiophen-2-yl)-2-methylpiperidine as a yellow oil (4.78 g, 99%).

Scheme I, step B: A solution of the crude *cis*-(±)-*N*-chloro-4-(4-methoxybenzo[*b*]thiophen-2-yl)-2-methylpiperidine (2.348 g, 7.93 mmol) in THF (80 mL) was treated with DBU (1.18 mL, 7.93 mmol). After stirring 17 h, the DBU salt was filtered off through a sintered funnel, rinsed with Et_2O, and the filtrate was concentrated under reduced pressure to give 4-(4-methoxybenzo[*b*]thiophen-2-yl)-2-methyl-3,4,5,6-tetrahydropyridine as a golden oil (2.3g, 99%) that was immediately used in the next step.

Scheme I, step C: To a solution of the crude 4-(4-methoxybenzo[*b*]thiophen-2-yl)-2-methyl-3,4,5,6-tetrahydropyridine (2.19 g, 8.44 mmol) in THF (38 mL) cooled to –78 °C in a dry ice / acetone bath, was added dropwise $BF_3 \bullet Et_2O$ (48%) (3.34 mL, 12.6 mmol) via a syringe. After stirring ten minutes, the solution was treated with 24.1 mL (33.77 mmol) of 1.4 M MeLi. The mixture was stirred for 16 h, then quenched with 100 mL of saturated aqueous NH_4Cl and 50 mL of H_2O. The mixture was then extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography [2.5 to 7% (2.0 M NH_3 in MeOH)/CH_2Cl_2] to give the title compound as an orange oil (0.713 g, 30%). IR (KBr) 2936, 1571, 1471, 1259, 1049 cm^{-1}. Ion Spray MS 276.2 $(M+H)^+$. $[\alpha]_D = 0$ (*c* 0.578, MeOH).

Example 2

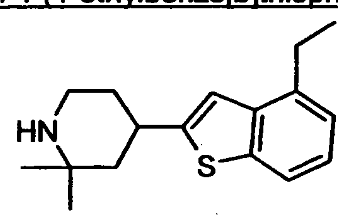
Preparation of 2,2-Dimethyl-4-(naphth-2-yl)piperidine.



Scheme I, steps A through C: In a manner analogous to the procedure described in example 1, the title compound is prepared from *cis*-(±)-4-(naphth-2-yl)-2-methylpiperidine.

Example 3

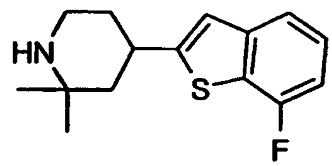
Preparation of 2,2-Dimethyl-4-(4-ethylbenzo[*b*]thiophen-2-yl)piperidine.



Scheme I, Steps A through C: In a manner analogous to the procedure described in example 1, the title compound is prepared from *cis*-(±)-4-(4-ethylbenzo[*b*]thiophen-2-yl)-2-methylpiperidine prepared in preparation 1.

Example 4

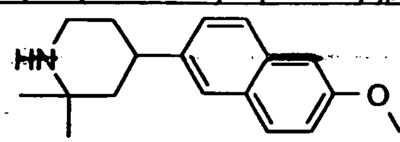
Preparation of 2,2-Dimethyl-4-(4-fluorobenzo[*b*]thiophen-2-yl)piperidine.



Scheme I, Steps A through C: In a manner analogous to the procedure described in example 1, the title compound is prepared from *cis*-(±)-4-(7-fluorobenzo[*b*]thiophen-2-yl)-2-methylpiperidine prepared in preparation 2.

Example 5

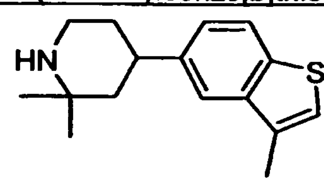
Preparation of 2,2-Dimethyl-4-(6-methoxynaphth-2-yl)piperidine.



Scheme I, Steps A through C: In a manner analogous to the procedure described in example 1, the title compound is prepared from (*cis*)-4-(6-methoxynaphth-2-yl)-2-methylpiperidine prepared in preparation 3.

Example 6

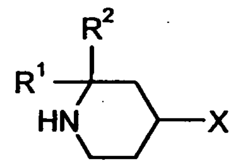
Preparation of 2,2-Dimethyl-4-(3-methylbenzo[*b*]thiophen-5-yl)piperidine.



Scheme I, Steps A through C: In a manner analogous to the procedure described in example 1, the title compound is prepared from (*cis*)-2-Methyl-4-(3-methylbenzo[*b*]thiophen-5-yl)piperidine prepared in preparation 4.

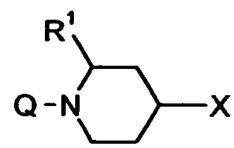
WE CLAIM:

1. A process for preparing a compound of formula I:



formula I

wherein R^1 and R^2 each independently represent C_1-C_4 alkyl; and X represents an alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle, comprising treating a compound of formula II:



formula II

wherein Q represents Cl or Br, with a suitable base followed by addition of a suitable Lewis acid and a compound of formula R^-M^+ wherein M^+ is a suitable cation.

2. The process according to claim 1 wherein the compound of formula II is in the CIS configuration.

3. The process according to claim 1 or claim 2 wherein Q is Cl.

4. The process according to any one of claims 1 to 3 wherein M^+ is lithium.

5. The process according to any one of claims 1 to 4 wherein the suitable base is DBU.

6. The process according to any one of claims 1 to 6 wherein the suitable Lewis acid is boron trifluoride either.

7. The process according to any one of claims 1 to 6 wherein R^1 and R^2 are each methyl.

8. The process according to any one of claims 1 to 7 wherein X is heterocycle or substituted heterocycle.

9. The process according to any one of claims 1 to 7 wherein X is aryl or substituted aryl.

10. The process according to any one of claims 1 to 7 wherein X is benzothiophene or substituted benzothiophene.

11. The process according to any one of claims 1 to 7 wherein X is benzofuran or substituted benzofuran.

12. The process according to any one of claims 1 to 7 wherein X is indole or substituted indole.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/32424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/12 C07D211/22 C07D409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HALL H K JR: "Steric Effects on the Base Strengths of Cyclic Amines" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 79, no. 19, 9 October 1957 (1957-10-09), pages 5444-5447, XP002164120 page 5445, column 1, paragraph 2 page 5446, column 2, paragraph 5	1-12
A	HOUBEN-WEYL: "Methoden der Organischen Chemie, vol. E14b: "Organische Stickstoff-Verbindungen mit einer C,N-Doppelbindung", Teil 1" 1990 , GEORG THIEME VERLAG , STUTTGART XP002164121 pages 229-231, chapter 1.1.2.2	1-12

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2001	04.05.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/32424

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOUBEN-WEYL: "Methoden der Organischen Chemie, vol. E16d: "Organische Stickstoffverbindungen IV", Teil II" 1992 , GEORG THIEME VERLAG , STUTTGART XP002164122 pages 1029-1041, chapter 5.1	1-12
A	HOUBEN-WEYL: "Methoden der Organischen Chemie, vol. XI/1: "Stickstoffverbindungen II", Teil 1" 1957 , GEORG THIEME VERLAG , STUTTGART XP002164123 page 333, chapter III(f)	1-12

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

International application No.
PCT/US 00/32424

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-12 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (partly)

Present claims 1-12 relate to a process defined by reference to a desirable characteristic or property (cf., the terms "suitable base", suitable Lewis acid" and "suitable cation").
Moreover the non-limiting expressions "substituted aryl" and "substituted heterocycle" add further clarity problems (it would appear that what can be regarded to be a "suitable base", a "suitable Lewis acid" etc. is also largely dependent on the nature of the substituent group X in the compounds of formula II).
The claims thus cover processes having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such processes.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the process by reference to a result to be achieved.
Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to a process wherein
the "substituted aryl" refers to a an aryl group as indicated on page 3, lines 9-10 of the present description optionally carrying substituents as given on page 3, line 31- page 4, line 4 of the present description,
the "substituted heterocycle" refers to a an heterocyclic group as indicated on page 3, lines 11-28 of the present description optionally carrying substituents as given on page 3, line 31- page 4, line 4 of the present description,
the "suitable base" is one selected from the bases as given on page 8, lines 5-6 and lines 11-15 of the present description,
the "suitable Lewis acid" is boron trifluoride etherate (cf., page 9, line 2 of the present description), and
the "suitable cation" is lithium (cf., page 9, line 3 of the present description).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.